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survival benefit, and identification of this subset would also have significant clinical benefit. Toward this end, we have used matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI MS) as a rapid, affordable and simple strategy that can be applied to the analysis of complex biological samples such as serum, urine and tissue. Peaks in the mass spectrum correspond to ions formed from relatively abundant species in the sample, predominantly peptides and proteins. We have used MALDI MS to study unfractionated, pretreatment sera to identify NSCLC patients with improved survival after treatment with the EGFR TKIs gefitinib and erlotinib(1). Mass spectra, independently acquired at two institutions, gave highly concordant results, and were used to generate an algorithm predictive of time to progression and survival. This prediction algorithm was then validated in a blinded manner in two independent cohorts of NSCLC patients treated with EGFR TKIs. This classification algorithm did not predict outcome in three independent cohorts of patients who did not receive treatment with EGFR TKIs. Thus, if upheld in prospective clinical trials, this simple, rapid, and inexpensive analysis of pre-treatment peripheral blood might be useful in selecting therapy for advanced non-small cell lung cancer patients.

1. Taguchi F, Solomon B, Gregorc V, et al. Mass Spectrometry to Classify NSCLC Patients for Clinical Outcome after Treatment with EGFR Tyrosine Kinase Inhibitors: A Multi-Cohort Cross Institutional Study. J Natl Cancer Inst 2007;In press.

M06-04 Molecular Predictors and Prognosticators, Mon, Sept 3, 10:30 - 12:00

Genomic signatures of prognosis in early stage non-small cell lung cancer

Tsao, Ming S.

Princess Margaret Hospital, Toronto, ON, Canada

Non-small cell lung cancer (NSCLC) constitutes approximately 80% of all lung cancers, and tumor stage is the primary determinant of prognosis for these patients (1). The term "early stage" has been commonly used to represent stage I and II patients. These are patients who have potentially curable disease by complete surgical resection. However, the overall prognosis of these early stage patients remains relatively poor with 5-year survival rates of 30-60% (2). Variation in survival largely reflects heterogeneity in the tumor biology, with some tumors having more aggressive growth and greater metastatic potential than others. While histology subtypes and grades demonstrate some impact on the prognosis of NSCLC patients, the overall differences are not sufficiently great to affect treatment decisions (3). An ability to identify molecular characteristics that can improve the classification of patient prognosis additional to tumor stage would provide the rationale for adjuvant therapy to patients with the significantly poorer prognosis. With recent trials showing that adjuvant chemotherapy significantly improve the survival of stage II-IIIA patients, the development of molecular prognostic markers has assume some urgency.

The first evidence that a molecular aberration in lung cancer can be a prognostic marker was the KRAS oncogene. Slebos et al (4) reported that oncogenic KRAS mutations occurred in 30% of lung adenocarcinoma and its presence defined a subgroup of patients with very poor prognosis. Since then, more than fifty retrospective and mostly institutional-based studies were conducted to validate this report, but they provided contradicting results. A meta-analysis on 23 PCR-based studies (2632 patients) involving NSCLC patients and 11 studies (1170 patients) involving only adenocarcinoma patients recorded RAS mutation hazard ratios (HR) of 1.39 (95% confidence interval 1.22 - 1.58; p=0.03) and 1.50 (95% CI 1.26-1.80; p=0.1), respectively (5). These results strongly suggest that RAS mutation is a poor prognostic marker in NSCLC patients. However, the only two studies that involved phase III randomized adjuvant clinical trial patients, the ECOG E4592 (6) and NCIC CTG JBR.10 (7) trials, failed to show a prognostic value for RAS mutation.

Similar to RAS, abnormal p53 protein expression and p53 gene mutations have been extensively investigated for their prognostic value in early stage resected NSCLC patients. Despite discrepancies among individual studies, results of two meta-analyses involving overlapping published data provided strong evidence that both abnormal p53 protein expression (positive immunohistochemistry) and p53 gene mutation are poor prognostic markers, and the impact appears greater in adenocarcinoma compared to squamous cell carcinoma (8, 9). Nevertheless, neither RAS and p53 mutation analyses nor p53 immunohistochemistry are routinely performed in clinical practice, as further evidence of their impact on patient selection for adjuvant chemotherapy is needed.

Over the last two decades, there has been an exponential growth in our knowledge of the nature of human genome, genes that make up our chromosomes, molecular signaling pathways that regulate cellular processes, and aberrations in the genetic and signaling networks in cancers and cancer cells. With completion of the human genome project, the identification of all 30-50 thousand human genes is nearly complete. Microarray technologies were developed to facilitate the evaluation of this new genetic information at a genome-wide scale. The first series of microarray studies in lung cancer demonstrated that gene expression profiling was able to distinguish different histological types of lung cancers (10, 11). These and other studies also reported that there are expression signatures that can identify patients with significantly different prognosis (12,13). However, it soon became apparent that the sets of prognostic signature genes from different studies showed minimal overlaps. Furthermore, analyses of a microarray dataset using different statistical or computational algorithms could yield different sets of putatively prognostic gene signatures (14,15). The apparent discrepancies between these studies were attributed putatively to variability in microarray platforms used, data processing, analytical algorithm and demographic differences in the patient cohorts studied. Nevertheless, these studies provided the important proof of principle that microarrays could yield biologically relevant information for defining tumor characteristics beyond histology. While the initial prognostic signatures are composed of hundreds to thousands of gene probes, validation of these microarray results using the more quantitative assay called reverse transcription quantitative polymerase chain reaction (RT-qPCR) led to the identification of smaller sets of prognostic gene classifiers, but further confirmation of the latter in separate cohorts of patients was challenging (16,17). More recently, seemingly more rational approaches to identify prognostic gene classifiers based on patients' extreme survival outcomes (18,19) or tumor cell biology (20) has revealed novel genomic classifiers that could be validated in independent patient cohorts. The fidelity of these classifiers in additional large independent patient/sample datasets generated in other laboratories remains to be confirmed.

While the above gene expression profiling studies are mRNA based, more recent efforts have used microarray platforms that can profile changes in genome wide gene copy number changes (array-comparative genomic hybridization/CGH) and single nucleotide polymorphisms (SNP) (21,22). Since DNA is more stable than RNA, these studies may be more easily performed using DNA isolated from formalin-fixed and paraffin embedded archival tumor samples. Array-CGH studies

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performed on DNA of lung cancer cell lines and primary tumors have demonstrated non-random and consistent gains and losses of genetic materials on various chromosomal arms (23-25). Large gains indicate gene amplification, some of which represent potential oncogenes. In contrast, genes that are commonly lost have a high probability of being tumor suppressor genes. One of the chromosomal arms that show a high frequency of genetic gains in non-small cell lung cancer is 5p (short arm). Zhu et al (26,27) has previously demonstrated that overexpression and/or high amplification of two genes located on 5p, Skp2 (5p13) and hTERT (5p15) are associated with poor prognosis in a subgroup of NSCLC patients. Future studies will likely identify additional genomic copy signatures that could be strong classifiers for patients with significantly different clinical outcomes.

References

1. Mountain CF: Revisions in the International system or staging lung cancer. Chest 1997;:1710-7.
2. Ponn RB, Lo Cicero J III, Daly BDT. Surgical treatment of non-small cell lung cancer. In: Shields TW, Lo Cicero III J, Ponn R, Rusch VW, eds. General thoracic surgery. 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2005:1548-87.
3. Sun Z, Aubry M-C, Deschamps C, et al. Histologic grade is an independent prognostic factor for survival in non-small cell lung cancer: An analysis of 5018 hospital- and 712 population-based cases. J Thorac Cardiovasc Surg 2006;131:1014-20.
4. Slebos RJC, Kibbelaar RE, Dalesio O, et al. K-RAS oncogene activation as a prognostic marker in adenocarcinoma of the lung. New Engl J Med 1990;323:561-5.
5. Mascaux C, Iannino N, Martin B, et al. The role of RAS oncogenes in survival of patients with lung cancer: a systematic review of the literature with meta-analysis. Br J Cancer 2005;92:131-9.
6. Schiller JH, Adak S, Feins R, et al. Lack of prognostic significance of p53 and K-ras mutations in primary resected non-small-cell lung cancer on E4592: A laboratory ancillary study on an Eastern Cooperative Oncology Group prospective randomized trial of postoperative adjuvant therapy. J Clin Oncol 2001;19:448-57.
7. Winton T, Livingston R, Johnson D, et al. Adjuvant vinorelbine and cisplatin post non-small cell lung cancer resection. New Engl J Med 2005;352:2589-97.
8. Mitsudomi T, Hamajima N, Ogawa M, et al. Prognostic significance of p53 alterations in patients with non-small cell lung cancer: A meta-analysis. Clin Cancer Res 2000;6:4055-63.
9. Steels E, Paesmans M, Berghmans T, et al. Role of p53 as a prognostic factor for survival in lung cancer: as systematic review of the literature with a meta-analysis. Eur Respir J 2001:18:705-19.
10. Bhattacharjee A, Richards WG, Staunton J, et al. Classification of human lung carcinomas by mRNA expression profiling reveals distinct adenocarcinoma subclasses. Proc Natl Acad Sci USA 2001;98:13790-5.
11. Garber ME, Troyanskaya OG, Schluens K, et al. Diversity of gene expression in adenocarcinoma of the lung. Proc Natl Acad Sci U S A 2001;98:13784-9.
12. Beer DG, Kardia SL, Huang CC, et al. Gene-expression profiles predict survival of patients with lung adenocarcinoma. Nat Med 2002;8:816-24.
13. Wigle DA, Jurisica I, Radulovich N, et al. Molecular profiling of non-small cell lung cancer and correlation with disease-free survival. Cancer Res 2002;62:3005-8.
14. Parmigiani G, Garrett-Mayer ES, Anbazhagan R, et al. A cross-study comparison of gene expression studies for the molecular classification of lung cancer. Clin Cancer Res 2004;10:2922-7.
15. Jiang H, Deng Y, Chen HS, et al. Joint analysis of two microarray gene-expression data sets to select lung adenocarcinoma marker genes. BMC Bioinformatics 2004, 5:81.
16. Endoh H, Tomida S, Yatabe Y, et al. Prognostic model of pulmonary adenocarcinoma by expression profiling of eight genes as determined by quantitative real-time reverse transcriptase polymerase chain reaction. J Clin Oncol 2004;22:811-9.
17. Blackhall FH, Wigle DA, Jurisica I, et al. Validating the prognostic value of marker genes derived from a non-small cell lung cancer microarray study. Lung Cancer 2004;46:197-204.
18. Potti A, Mukherjee S, Petersen R, et al: A genomic strategy to refine prognosis in early-stage non-small-cell lung cancer. N Engl J Med 2006;355:570-80.
19. Lu Y, Lemon W, Liu PY, et al. A gene expression signature predicts survival of patients with stage I non-small cell lung cancer. PLoS Med 2006;3:e467.
20. Chen HY, Yu SL, Chen CH, et al. A five-gene signature and clinical outcome in non-small-cell lung cancer. N Engl J Med 2007;356:11-20.
21. Lockwood WW, Chari R, Chi B, et al. Recent advances in array comparative genomic hybridization technologies and their applications in human genetics. Eur J Hum Genetics 2006;14:139-48.
22. Jacobs S, Thompson ER, Nannya Y, et al. Genome-wide, high resolution detection of copy number, loss of heterogeneity, and genotypes from formalin-fixed paraffin-embedded tumor tissue using microarrays. Cancer Res 2007;67:2544-51.
23. Garnis C, Davies JJ, Buys TPH, et al. Chromosome 5p Aberrations Are Early Events In Lung Cancer: Implication Of Glial Cell Line-Derived Neurotrophic Factor In Disease Progression. Oncogene 2005;24:4806-12.
24. Garnis C, Lockwood WW, Vucic E, et al. High resolution analysis of non-small cell lung cancer cell lines by whole genome tiling path array CGH. Int J Cancer 2006; 118:1556-64.
25. Shibata T, Uryu S, Kokubu A, et al. Genetic classification of lung adenocarcinoma based on array-based comparative genomic hybridization analysis: Its association with clinicopathologic features. Clin Cancer Res 2005;11:6177-85.
26. Zhu CQ, Blackhall FH, Pintilie M, et al. Skp2 is commonly amplified in non-small cell lung carcinoma and its overexpression in tumors with ras mutation is a poor prognostic marker. Clin Cancer Res 2004;10:1984-91.
27. Zhu CQ, Cutz JC, Liu N, et al. Amplification of telomerase (hTERT) gene is a poor prognostic marker in non-small-cell lung cancer. Br J Cancer 2006;94:1452-9.

Session M07: Debate in Lung Cancer Surgery

M07-01 **Debate in Lung Cancer Surgery, Tue, Sept 4, 10:30 - 12:00**

Pneumonectomy versus sleeve resection for the management of resectable lung cancer

Deslauriers, Jean

Centre de pneumologie et Service de chirurgie thoracique, Hôpital Laval, Sainte-Foy, Canada

Sleeve lobectomy for lung cancer was first described as a compromise operation for patients whose pulmonary reserve was considered inadequate to permit pneumonectomy. Since then, several authors have suggested that sleeve resection may provide as good if not better results than pneumonectomy in selected cases of primary lung cancer involving the proximal bronchial tree. Whether sleeve resection is radical enough and indicated for patients who could tolerate pneumonectomy continues to be debated among thoracic surgeons and indeed there are only a handful of reports of clinical series comparing operative mortality, survival, and sites of recurrences between these procedures (Table 1).

Table 1 - Comparison of survival between sleeve resection and pneumonectomy

Authors (yr)	No pts	5 year survival (%)	
		Sleeve resection	Pneumonectomy
Gaissert (1996)	128	42 %	44 %
Yoshino (1997)	58	66 %	59 %
Suen (1999)	200	38 %	36 %
Ludwig (2005)	310	39 %	27 %
Takeda (2006)	172	54 %	33 %

Operative mortality, survival, and sites of recurrences were compared in 1,346 consecutive patients who underwent pneumonectomy (N : 1,046) or sleeve resection in our institution over a 25-year interval (Table 2).

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